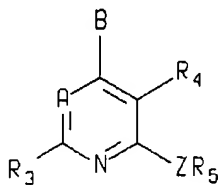


MARKED UP COPY OF AMENDED CLAIMS
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1.(TWICE AMENDED)

A compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

A is -CR₇;

B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁, -CHR₁OR₂, -CHR₂SR₁, -C(S)R₂, -C(O)R₂, -CHR₂NR₁R₂, -CHR₁NHR₂, -CHR₁N(CH₃)R₂, or -NR₁₂NR₁R₂;

Z is NH, O, S, -N(C₁-C₂ alkyl), -NC(O)CF₃, or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl, or -C(R₁₃R₁₄) is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R₅, which ring optionally includes two or three further hetero members selected independently from oxygen, nitrogen, NR₁₂, and S(O)_m, and optionally includes from one to three double bonds, and is optionally substituted with halo, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), NH₂, NHCH₃, N(CH₃)₂, CF₃, or OCF₃, with the proviso that said ring does not include any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and does not include more than two oxygen or S(O)_m heterologous members;

R₁ is C(O)H, C(O)(C₁-C₆ alkyl), C(O)(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), C(O)(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C(O)(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -C(O)(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), or -O-aryl, or -O-(C₁-C₆ alkylene)-aryl; wherein said aryl, C₄-C₈ heterocycloalkyl, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkylene, and C₁-C₆ alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R₈ independently selected from the group consisting of C₁-C₄ alkyl, -C₃-C₈ cycloalkyl, hydroxy, chloro, bromo, iodo, CF₃, -O-(C₁-C₆ alkyl), -O-(C₃-C₅ cycloalkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(R₂₄)(R₂₅), -N(R₂₄)(R₂₅), -S(C₁-C₄ alkyl), -S(C₃-C₅ cycloalkyl), -N(C₁-C₄alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, -SO(C₁-C₄ alkyl) and -SO₂(C₁-C₄

alkyl); and wherein the C₁-C₆ alkyl, C₁-C₆ alkylene, C₅-C₈ cycloalkyl, C₅-C₈ cycloalkylene, and C₅-C₈ heterocycloalkyl moieties of R₁ may optionally independently include from one to three double or triple bonds; and wherein the C₁-C₄ alkyl moieties and C₁-C₆ alkyl moieties of R₈ can optionally independently be substituted with hydroxy, amino, C₁-C₄ alkyl, aryl, -CH₂-aryl, C₃-C₅ cycloalkyl, or -O-(C₁-C₄ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally include one or two double or triple bonds; and wherein each heterocycloalkyl group of R₁ includes from one to three heteromoieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

R₂ is hydrogen, C₁-C₁₂ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, -(C₁-C₆ alkylene)aryl, or -(C₃-C₈ cycloalkylene)(aryl); wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)⁻, CN, and NO₂; and wherein the C₁-C₁₂ alkyl, -(C₁-C₆ alkylene), -(C₅-C₈ cycloalkyl), -(C₅-C₈ cycloalkylene), and -(C₅-C₈ heterocycloalkyl) moieties of R₂ may optionally independently include from one to three double or triple bonds; and wherein each heterocycloalkyl group of R₂ includes from one to three heteromoieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

or when R₁ and R₂ are as in -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₁R₂ or -NR₁R₂, R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally include one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₄ alkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), wherein one of said one to three substituents can further be selected from phenyl;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, NH₂, NH(C₁-C₂ alkyl), N(CH₃)₂, -NHCOCF₃, -NHCH₂CF₃, S(O)_m(C₁-C₄ alkyl), CONH₂, -CONHCH₃, CON(CH₃)₂, -CF₃, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ alkyl, C₃-C₅ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR₂₄, C₁-C₆ alkoxy, -O-(C₃-C₅ cycloalkyl), -O-(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -O-(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), -CH₂SC(S)O(C₁-C₄ alkyl), -CH₂OCF₃, CF₃, amino, nitro, -NR₂₄R₂₅, -(C₁-C₄ alkylene)-OR₂₄, -(C₁-C₄ alkylene)Cl, -(C₁-C₄ alkylene)NR₂₄R₂₅, -NHCOR₂₄, -NHCONR₂₄R₂₅, -C=NOR₂₄, -NHNOR₂₄R₂₅, -

$S(O)_mR_{24}$, $-C(O)R_{24}$, $-OC(O)R_{24}$, $-C(O)CN$, $-C(O)NR_{24}R_{25}$, $-C(O)NHNHNR_{24}R_{25}$, and $-COOR_{24}$, wherein the alkyl and alkylene groups of R_4 may optionally independently include one or two double or triple bonds and may optionally independently be substituted with one or two substituents R_{10} independently selected from hydroxy, amino, $-NHCOCH_3$, $-NHCOCH_2Cl$, $-NH(C_1-C_2 \text{ alkyl})$, $-N(C_1-C_2 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, $-COO(C_1-C_4 \text{ alkyl})$, $-COOH$, $-CO(C_1-C_4 \text{ alkyl})$, C_1-C_6 alkoxy, C_1-C_3 thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

R_5 is aryl or heteroaryl and is substituted with from one to four substituents R_{27} independently selected from halo, C_1-C_{10} alkyl, $-(C_1-C_4 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_1-C_4 \text{ alkylene})(C_4-C_8 \text{ heterocycloalkyl})$, $-(C_3-C_8 \text{ cycloalkyl})$, $-(C_4-C_8 \text{ heterocycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_4-C_8 \text{ heterocycloalkyl})$, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, nitro, cyano, $-NR_{24}R_{25}$, $-NR_{24}COR_{25}$, $-NR_{24}CO_2R_{26}$, $-COR_{24}$, $-OR_{25}$, $-CONR_{24}R_{25}$, $-CO(NOR_{22})R_{23}$, $-CO_2R_{26}$, $-C=N(OR_{22})R_{23}$, and $-S(O)_mR_{23}$; wherein said C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, $(C_1-C_4 \text{ alkylene})$, $(C_3-C_8 \text{ cycloalkyl})$, $(C_3-C_8 \text{ cycloalkylene})$, and $(C_4-C_8 \text{ heterocycloalkyl})$ groups can be optionally substituted with from one to three substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, $(C_1-C_4 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, C_1-C_4 haloalkyl, hydroxy, C_1-C_6 alkoxy, nitro halo, cyano, $-NR_{24}R_{25}$, $-NR_{24}COR_{25}$, $-NR_{24}CO_2R_{26}$, $-COR_{24}$, $-OR_{25}$, $-CONR_{24}R_{25}$, CO_2R_{26} , $-CO(NOR_{22})R_{25}$, and $-S(O)_mR_{23}$; and wherein two adjacent substituents of the R_5 group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R^5 , which ring optionally can include one, two, or three heterologous members independently selected from O, $S(O)_m$, and N, but not any $-S-S-$, $-O-O-$, $-S-O-$, or $-N-S-$ bonds, and which ring is optionally substituted with C_1-C_4 alkyl, C_3-C_8 cycloalkyl, $-(C_1-C_4 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, C_1-C_4 haloalkyl, nitro, halo, cyano $-NR_{24}R_{25}$, $-NR_{24}COR_{25}$, $-NR_{24}CO_2R_{26}$, $-COR_{24}$, $-OR_{25}$, $-CONR_{24}R_{25}$, CO_2R_{26} , $-CO(NOR_{22})R_{25}$, and $-S(O)_mR_{23}$; wherein one of said one to four optional substituents R_{27} can further be selected from $-SO_2NH(C_1-C_4 \text{ alkyl})$, $-SO_2NH(C_1-C_4 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $-SO_2NH(C_3-C_8 \text{ cycloalkyl})$, $-SO_2NH(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, $-SO_2N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, $-SO_2NH_2$, $-NHSO_2(C_1-C_4 \text{ alkyl})$, $-NHSO_2(C_3-C_8 \text{ cycloalkyl})$, $-NHSO_2(C_1-C_4 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, and $-NHSO_2(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$; and wherein the alkyl, and alkylene groups of R_5 may independently optionally include one double or triple bond;

R_6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, $-(C_1-C_6 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, or $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

R_7 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, $-O(C_1-C_2 \text{ alkyl})$, $-O(\text{cyclopropyl})$, $-COO(C_1-C_2 \text{ alkyl})$, $-COO(C_3-C_8 \text{ cycloalkyl})$, $-OCF_3$, CF_3 , $-CH_2OH$, or CH_2OCH_3 ;

R_{11} is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl;

R_{22} is independently at each occurrence selected from hydrogen, C_1-C_4 alkyl, C_1-C_4

haloalkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl);

R₂₃ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

R₂₄ and R₂₅ are independently at each occurrence selected from hydrogen, -C₁-C₄ alkyl, C₁-C₄ haloalkyl, especially CF₃, -CHF₂, CF₂CF₃, or CH₂CF₃, -(C₁-C₄ alkylene)OH, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₃-C₅ cycloalkyl), C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -C₄-C₈ heterocycloalkyl, -(C₁-C₄ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl), wherein the -C₄-C₈ heterocycloalkyl groups can each independently optionally be substituted with aryl, CH₂-aryl, or C₁-C₄ alkyl, and can optionally include one or two double or triple bonds; or, when R₂₄ and R₂₅ are as NR₂₄R₂₅, -C(O)NR₂₄R₂₅, -(C₁-C₄ alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 membered heterocyclic ring optionally including one or two further hetero members independently selected from S(O)_m, oxygen, nitrogen, and NR₁₂, and optionally including from one to three double bonds;

R₂₆ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocycloalkyl groups of the compound of formula I [~~II~~, ~~III~~] do not include any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and do not include more than two oxygen or S(O)_m heterologous members.

9. (AMENDED) A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthymia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; ~~cancer~~; irritable bowel syndrome~~[-Crohn's disease]~~; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; ~~[human immunodeficiency virus infections]~~ neurodegenerative diseases such as

Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; ~~[eating disorders such as anorexia and bulimia nervosa;]~~ hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; ~~[obesity; infertility;]~~ head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis~~[-]~~ and premature birth~~[- hypoglycemia, and Syndrome X]~~ in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

10. (AMENDED) A method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; ~~[cancer;]~~ irritable bowel syndrome~~[- Crohn's disease]~~; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; ~~[human immunodeficiency virus infections;]~~ neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; ~~[eating disorders such as anorexia and bulimia nervosa;]~~ hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; ~~[obesity; infertility;]~~ head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence;

senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis[;] and premature birth[; hypoglycemia, and Syndrome X] in a mammal or bird, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder or condition.

17. A pharmaceutical composition for treating a condition comprising a compound of claim 1 in an amount effective to treat said condition and a pharmaceutically acceptable carrier, wherein said condition is selected from the group consisting of:

- a) abnormal circadian rhythm;
- b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said ~~[CRF-antagonist]~~ compound of claim 1; and
- c) emesis.